The Current Role of Whole Brain Radiation Therapy in Non–Small Cell Lung Cancer Patients

REVIEW ARTICLE

The Current Role of Whole Brain Radiation Therapy in Non-Small Cell Lung Cancer Patients

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ABSTRACT

The incidence of brain metastases has increased in patients with NSCLC as a result of better systemic disease control and advances in imaging modalities. Whole brain radiotherapy (WBRT) has been the mainstay treatment of multiple symptomatic brain metastases for years. A number of recent publications have questioned its place in the absence of a survival and quality of life benefit and the possible risk for long-term neurotoxicity. Omission or deferral of WBRT and strategies consisting of stereotactic radiosurgery or delivery of systemic therapies alone are being proposed more and more. However, critical analysis of the literature shows that WBRT still has relevant indications in well-selected patients. Within this review, we discuss the place of WBRT in the modern management of patients with NSCLC.

Keywords: Radiotherapy; Stereotactic radiotherapy; Brain irradiation; Targeted therapy; *EGFR* mutation; *ALK* translocation

Introduction

Brain metastases (BMs) are frequent in the natural history of malignant tumors. In patients with NSCLC, BMs occur in up to 22% of patients at the time of initial diagnosis, and BM will develop in approximately 40% of patients during their disease.[1,2] Furthermore, the incidence and prevalence of BMs are rising given the advances in imaging methods and improvements in systemic control. The latter has resulted in a longer survival and, consequently, more time for development of BMs. With subsequent deleterious effects on many critical neurologic functions, BM is an indicator of poor outcome.[3] In the past years, the backbone of focal treatments included surgery and/or whole brain radiotherapy (WBRT).[4,5] Recent trials have questioned the relevance of WBRT at a time when radiosurgery or stereotactic radiotherapy (SRS) is being used with increasing frequency and when newer efficient therapies such as targeted molecular compounds and immunotherapies have become available.[6] Longer survival observed in patients with stage IV NSCLC has also led to more careful consideration of the risks for development of debilitating late complications possibly induced by brain irradiation.[7] On the other hand, WBRT may still have a role when delivered to appropriate patients.[8–10] This narrative review reappraises the role of WBRT as a part of the actual multimodal management of patients with NSCLC.

Arguments for Contemporary WBRT Indications

Patients Unsuitable for SRS and/or Surgery

According to significant prognostic factors (age, Karnofsky performance score [KPS], presence of

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extracranial metastases, and number of BMs) included in the diagnosis-specific graded prognostic assessment (DS-GPA), and recursive partitioning analysis (RPA) (the latter including the primary tumor under control but not the number of BMs), survival in NSCLC ranges from 3 to 14.8 months.[3] Prognostic scores have been incorporated into treatment decisions, and focal interventions should preferentially be delivered to patients with a good prognosis. WBRT alone has usually been the preferred treatment for patients with multiple BMs unsuitable for SRS and/or neurosurgical treatment. In this population, "palliative" WBRT was generally thought to improve quality of life (QoL) (in patients with neurologic symptoms) and possibly survival in comparison with best supportive care.[11,12]

However, this was not prospectively assessed until the recently published noninferiority phase 3 QUARTZ trial (Table 1). In this study, 538 patients with NSCLC were randomized to dexamethasone and optimal supportive care with and without WBRT (20 Gy in five daily fractions). The primary end point was quality-adjusted life-years (QALYs). Patients were included when the physician and or the multidisciplinary team were "uncertain about the potential benefit of WBRT." Systemic treatments were allowed, but details were not reported in the article, suggesting that some patients had no systemic treatment options. The conclusion was that WBRT did not improve QALYs (there were 46.4 QALY days for the group receiving optimal supportive care plus WBRT versus 41.7 QALY days for the other group), overall survival (OS) (hazard ratio [HR] = 1.06, 95% confidence interval [CI]: 0.90–1.26) or QoL. One limitation of this trial could be that it included a large proportion of patients with poor prognosis, explaining the dismal median survival of 9 weeks. More than a third of the included population had RPA class III and did not benefit from WBRT. The multivariable analysis indicated that patients younger than 60 years and with a KPS of 70 or higher, absence of extracranial metastases, and controlled primary tumor (i.e., those in RPA class I/good DS-GPA class) had superior outcomes with WBRT.[13] This difference did not reach statistical significance, except for younger patients ($p = 0.006$), but the trial was also not powered to detect these differences. On the basis of these data, WBRT remains a valid option for patients with NSCLC-GPA with a score of at least 1.5 or patients in RPA class I, which corresponds to a median survival of 5.5 months.[3]

Adjuvant WBRT after SRS

SRS (in single or multiple fractions) has become a common therapeutic modality for patients with a good prognosis and limited brain tumor volume. Metastases are

Table 1. Main Phase III Trials Assessing Whole Brain Radiotherapy

Indication	First Author	Patients with NSCLC, n%	Primary End Point	Follow-up	Brain Local Failure	Brain Distant Failure	Overall Intracranial Failure	Disease-Free Survival	Overall Survival
Supportive care	Mulvenna[13]	538 (100) (WBRT: 269; obs: 269)	QALYs	NP	NP	NP	NP	NP	WBRT: 9.2 wk vs. obs: 8.5 wk; $p = 0.8$
Postop care	Patchell[14]	95 (62) (WBRT: 49; obs: 46)	Brain recurrence	43 wk	WBRT: 10% vs. obs: 46%; $p < 0.01$	WBRT: 14% vs. obs: 37%; $p < 0.01$	WBRT: 18% vs. obs: 70%; $p < 0.001$	NP	WBRT: 48 wk vs. obs: 43 wk; $p = 0.39$
PCI	Gore[15]	356 (100) (WBRT: 16; obs: 177)	Overall survival	NP	NP	NP	WBRT: 7.7% vs. obs: 18% (1 year); $p = 0.004$	WBRT: 54.6% vs. obs: 51.2%. (1 year); $p = 0.11$	WBRT: 75.6% vs. obs: 76.9% (1 year); $p = 0.86$
	Li[16]	156 (100) (WBRT: 81; obs: 75)	Disease-free survival	68.1 mo	NP	NP	WBRT: 20.3% vs. obs: 49.9% (5-y); $p < 0.001$	WBRT: 28.5 vs. obs: 21.2 mo (median); $p = 0.11$	WBRT: 31.2 vs. obs: 27.4 mo (median); $p = 0.31$

WBRT, whole brain radiotherapy; QALY, quality-adjusted life-years; NP, not provided; PCI, prophylactic cranial irradiation; obs, observation; postop: postoperative.

usually small (< 3 cm) and well defined. SRS alone (without WBRT) is feasible as the initial treatment for patients with five to 10 BMs. In a prospective nonrandomized study, patients with five to 10 BMs did not seem to fare worse than those with two to four BMs in terms of OS, intracranial tumor control, neurologic deterioration and death, leukoencephalopathy, or salvage treatment.[17] An ongoing randomized trial comparing SRS and WBRT for patients with four to 10 BMs (NCT02353000) will, it is hoped, better define the role of SRS in this setting. It should additionally be noted that SRS does not improve survival, except in the subgroup of patients with a single BM that was also treated with WBRT. In this 1:1 randomized phase III trial (Radiation Therapy Oncology Group [RTOG] 9508 [N = 333, 63% with lung cancer]), WBRT with or without the addition of SRS was evaluated. The patients with a single BM treated with WBRT plus SRS had an OS of 6.5 months compared with 4.9 months for those treated with WBRT only ($p = 0.0393$). Moreover, regardless of number of BMs, at 6 months those in the SRS arm had stable or improved performance status compared with those in the WBRT arm (43% versus 27% [$p = 0.03$]).[18]

Meanwhile, the impact of adjuvant WBRT after SRS in patients with a limited number of BMs was assessed through four randomized trials.[19–22] The four studies consistently reported a significantly decreased rate of brain failure, including intracranial distant and local failures, with WBRT (Table 2). The conservative strategy consisting of SRS without WBRT was associated with high rates of central nervous system (CNS) tumor failures (50%–76% versus 15%–47% with WBRT). The advantage in brain control provided by adjuvant WBRT, however, did not translate into an improvement in OS and demonstrated a detrimental effect on neurocognitive function (as measured by the Mini–Mental State Examination score at 12 months; Hopkins Verbal Learning Test [HVLT]–Revised score at 4 months; Late Effects Normal Tissue Task Force Subjective, Objective, Management, Analytic Scales scores, and cognitive test scores, [see Table 2]). Two trials even suggested a trend toward inferior survival with the addition of WBRT, including the recently reported Alliance trial.[20,22] In the latter trial, 213 patients with one to three BMs (68% lung primary) were randomly assigned to SRS plus WBRT or SRS alone. In the evaluated patients (half of the population), 3 months after completion of treatment less cognitive deterioration was found with SRS alone (40 of 63 patients [63.5%]) than with SRS combined with WBRT (44 of 48 patients [91.7%]) (a difference of –28.2% [$p < 0.001$]). Intracranial tumor control rates were increased with the addition of WBRT as compared with SRS alone (85% versus 50% at 12 months) whereas OS was not (HR = 1.02). On the basis of these data, the American Society for Radiation Oncology expressed reservations regarding the systematic use of adjuvant WBRT.[23]

Several limitations can still be highlighted in the interpretation of these trials. First, most patients succumbed from systemic progression or from other causes, and this may not have been properly detected in survival analyses. Second, salvage therapies, including WBRT in 12% to 33% of patients undergoing SRS (and/or repeated SRS and/or the addition of newer more effective systemic therapies), may have benefitted patients randomized to SRS. Third, the patients who benefitted from WBRT seemed to be those with a favorable prognosis. A secondary analysis of the Japanese trial JROSG 99-1 demonstrated a survival benefit for the subgroup of patients with NSCLC displaying a favorable DS-GPA score (2.5–4) and treated with SRS and WBRT versus with SRS alone (16.7 months versus 10.6 months, respectively [$p = 0.04$]).[24] Furthermore, most trials did include patients with different primary tumors, and information regarding driver mutations was not known.

Postoperative Radiation Therapy

Postoperative WBRT has been assessed for patients with a single resected BM in a randomized trial by Patchell et al.[14] (see Table 1). In that study, 95 patients (60 cases of lung cancer) were enrolled, with 49 patients assigned to the WBRT arm and 46 patients to the observation arm. Postoperative radiation prevented brain recurrence at the original site (10% versus 46%) and distant brain recurrence (14% versus 37%; overall brain recurrence 18% with WBRT versus 70% without WBRT). Although fewer neurologic-related deaths were observed with WBRT, there was no difference in OS.

SRS has been largely used as a postoperative radiation modality despite the absence of a high level of evidence. A multi-institutional randomized trial with 194 patients and one to four BMs was recently presented at the 2016 American Society for Radiation Oncology meeting. Patients were randomized to SRS (dose not provided) or WBRT after surgical resection of one lesion. Most patients (77%) had a single BM, and a lung tumor was the primary site for more than half of the patients (n = 114 [59%]). With a median follow up of 15.6 months, there was no survival difference: the median OS times with SRS or WBRT were 11.5 months and 11.8 months ($p = 0.65$), respectively. The rate of cognitive deterioration at 6 months was higher after WBRT (85.7%) than after SRS (53.8%) ($p = 0.0006$). WBRT did provide higher overall intracranial tumor control: the rates at 6 and 12 months were 90.0% and 78.6% with WBRT versus 74.0% and 54.7% with SRS ($p < 0.0001$). However, QoL was superior in the SRS arm.[25] Future studies should evaluate whether WBRT still has a role in patients with a high risk for brain relapse, especially

Table 2. Addition of Whole Brain Radiotherapy after Radiosurgery in Phase III Trials

	Study									
	Aoyama[19]		Chang[20]		Kocher[21]				Brown[22]	
Indicator	SRS + WBRT	SRS	SRS + WBRT	SRS	Surgery + WBRT	SRS + WBRT	Surgery	SRS	SRS + WBRT	SRS
Patients, n (% with NSCLC)	65 (66)	67 (67)	28 (53)	30 (57)	81 (54)	99 (54)	79 (52)	100 (52)	102 (65)	111 (72)
Primary end point	OS		Neurocognitive function		Duration functional independence				Cognitive deterioration at 3 mo	
Neurocognitive function assessment	MMSE score at 12 mo: 28	27	Drop in HVLT-R total recall at 4 mo: 52%	24%	LENT/SOMA scales				Cognitive deterioration at 3 mo: 91.7%	63.5%
RPA										
1	17%	12%	11%	23%	NP	NP	NP	NP	NP	NP
2	83%	43%	89%	77%	NP	NP	NP	NP	NP	NP
GPA										
0-1	NP	NP	10%	10.7%	NP	NP	NP	NP	NP	NP
1.5-2	NP	NP	63%	67.9%	NP	NP	NP	NP	NP	NP
3	NP	NP	17%	17.9%	NP	NP	NP	NP	NP	NP
3-5	NP	NP	10%	3.5%	NP	NP	NP	NP	NP	NP
Salvage WBRT	0%	16.4%	0%	33%	3% (surgery or SRS + WBRT)	NP	NP	33% (surgery or SRS)	1%	11.7%
Local brain failure	11%	27%	0%	33%	27%	19%	59%	31%	9.9%	27.2%
Intracranial distant failure	42%	64%	27%	55%	23%	33%	42%	48%	7.7%	24.8%
Any brain failure	47%	76%	27%	73%	NP	NP	NP	NP	15.4%	49.5%
Neurologic death	22.8%	19.3%	risk for neurological death with SRS + WBRT vs. SRS: HR = 2.1, $p = 0.15$		28% (surgery or SRS + WBRT)	NP	NP	44% (surgery or SRS)	NP	NP
OS	7.5 mo	8 mo	5.7 mo	15.2 mo	10.7 mo			10.9 mo	7.4 mo	10.4 mo

SRS, radiosurgery; WBRT, whole brain radiotherapy; OS: overall survival; MMSE, Mini-Mental State Examination; HVLT-R, Hopkins Verbal Learning Test-Revised; LENT, late effects of normal tissue; SOMA, subjective, objective, management, analytic; RPA, recursive partitioning analysis; NP, not provided; GPA, graded prognostic assessment; HR, hazard ratio.

those without a competing risk for death from extracranial metastases. In a large single institutional database with 528 patients, trimodality treatment regimen (surgery plus SRS plus WBRT) was associated with a higher median survival than surgery plus SRS or SRS alone and may be considered for patients with a favorable prognosis (DS-GPA score >2.5).[26] Potential neurocognitive toxicity results in this setting are awaited.

PCI

Another subset of patients with NSCLC who may benefit from WBRT are those with microscopic BM and a low extracranial tumor burden. This hypothesis may be extrapolated from two recent randomized trials investigating prophylactic cranial irradiation (PCI) in locally advanced patients with NSCLC who had virtually no remaining systemic disease (see Table 1). Both trials reported a reduction in BM occurrence after PCI, but without effect on survival outcomes. RTOG 0214 closed early because of slow accrual (356 enrolled patients of 1058 initially planned).[15] Patients with stage III NSCLC without progression after locoregional thoracic treatment (surgery and/or radiation therapy with or without chemotherapy) were randomly assigned to PCI or observation. Of note, follow-up included systematic brain imaging (at 6, 12, 24, 36, and 48 months and then yearly) after treatment, and this is not current practice in most centers.[27] At 1 year, PCI decreased the rate of BM (7.7% with PCI versus 18% with observation [$p = 0.004$]) without a survival benefit. Neurocognitive function and QoL results were subsequently reported. Patients who underwent PCI had no Mini–Mental State Examination score or QoL deterioration, although a decline in memory (according to the HVLT) was observed at 1 year.[28] Long-term results of this trial are awaited. The second trial compared PCI with observation in patients with resected stage IIIA-N2 NSCLC after adjuvant chemotherapy.[16] The actuarial 5-year BM rate was 20.3% with PCI versus 49.9% in the other group (HR = 0.28, $p < 0.001$). The PCI group had significantly longer disease-free survival (the primary end point): 28.5 months versus 21.5 months (HR = 0.6, $p = 0.037$). OS was not significantly improved in the PCI arm (31.2 months versus 27.4 months [$p = 0.31$]). However, the trial was terminated early after inclusion of 156 patients (of 254 initially planned), and no firm conclusion can be drawn given the lack of power. A subsequent trial (NVALT-11/DLCRG-02) assessing PCI in NSCLC was presented at the American Society of Clinical Oncology annual meeting this year. The primary objective was to determine whether PCI decreases the proportion of patients in whom symptomatic BMs develop at 24 months. Initially, 300 patients had to be randomized to detect a 17% decrease in the PCI arm with a 90% power. Because of slow accrual, 175 patients were randomized and it was decided to stop accrual. With a median follow-up of 48.5 months, the proportion of patients with symptomatic BM (the primary end point) was 4.6% in the PCI arm and 28.4% in the control arm ($p < 0.00001$). Median OS was 24.2 months in the PCI arm versus 21.9 months in the control arm ($p = 0.52$).[29]

Comparison with the SCLC model is interesting because it may help us understand some issues related to WBRT in NSCLC. PCI in SCLC was the only brain radiotherapy method leading to improvement in survival.[30,31] One should be aware that use of PCI in SCLC was controversial until the publication of the meta-analysis based on individual data, which included 987 patients with a complete response after chemotherapy.[30] In fact, most randomized trials demonstrated only a reduction in the rate of incidence of BM.[7] The European Organization for Research and Treatment of Cancer trial was the sole trial to report a benefit in OS for extensive-stage disease in response to induction therapy.[31] Interestingly, opponents of PCI at that time argued about the absence of survival benefit and long-term sequelae. PCI is now a standard in patients with SCLC with good response to frontline treatment in spite of prospective data mentioning increased adverse effects. In the randomized trial PCI 99-01 comparing the PCI dose of 25 or 36 Gy in 720 patients with limited SCLC, mild but significant deteriorations of communication deficit, fatigue, intellectual deficit, and memory loss were detected across time.[32] The QoL analysis of the European Organization for Research and Treatment of Cancer trial also reported a negative impact of PCI at 6 weeks.[33] It should be acknowledged that the risk for development of BM in patients with SCLC is probably higher than that for patients with NSCLC. PCI may thus be especially useful in patients with NSCLC with a theoretically higher BM risk (e.g., young, female, adenocarcinoma, and high–N status patients).

Combination of WBRT with Systemic Treatments

Patients with Targetable Driver Mutations

Over the past decade, major advances have been made in the understanding of NSCLC molecular biology. *EGFR* mutations and ALK receptor tyrosine kinase gene (*ALK*) translocation represent tumor driver mutations that dramatically predict response to specific tyrosine kinase inhibitors (TKIs) in patients with stage IV adenocarcinomas. Those patients consequently have a natural history and a prognosis that differ completely from those of patients with wild-type tumors.[34] An update of the GPA score (GPA for Lung Cancer Using Molecular Markers) integrating molecular markers *EGFR* and *ALK* was recently proposed.[35] Data from 2186 patients (time

period 2006–2014) with NSCLC and newly diagnosed BM (1521 adenocarcinomas and 665 nonadenocarcinomas) was analyzed. Significant prognostic factors included the original four factors plus *EGFR* and *ALK* alterations in patients with adenocarcinoma. The median OS was 12 months, but patients with NSCLC-adenocarcinoma with a Lung-molGPA score of 3.5 to 4.0 had an OS of nearly 4 years. Therefore, future studies should be designed taking these new clinically relevant parameters into account.

Although *EGFR/ALK* mutations/translocations in patients with NSCLC are associated with improved outcome when those patients are treated with TKI, there is debate as to whether BMs are prone to develop in them versus in patients with wild-type tumors. A retrospective Chinese study on 1063 patients with NSCLC suggested that those harboring mutations involving *EGFR* exon 19 (deletion) but not exon 21 were at higher risk for BM than those with wild-type tumors.[36] Eichler et al. demonstrated that patients bearing *EGFR* mutations were more likely to have multiple BMs, but there was no difference in the rate of leptomeningeal metastases.[37] Similarly, a study on *ALK*-translocated tumors before the era of anti-ALK TKI showed an increased rate of intracranial failure.[38] Other teams conversely found no difference or a decrease in BM occurrence between wild-type and *EGFR/ALK* NSCLC at baseline evaluation.[39,40] In any case, patients with a driver mutation and long-term survival are especially prone to development of BM, as in patients with a survival beyond 5 years, the percentage of patients with BM increases to 52.9%.[41]

First-generation TKIs targeting the *EGFR* and *ALK* pathways (erlotinib, gefinitib, and crizotinib) demonstrated a major response rate and progression-free survival benefit compared with conventional chemotherapy.[42–44] Encouraging results were also reported in the CNS with these targeted therapies. However, strategies based exclusively on TKIs without local therapy have led to inferior intracranial control (11%–26% versus 50%–77% for patients with NSCLC receiving chemotherapy).[45] The high rate of intracranial failure is attributable to both poor intracranial penetration of especially first-generation TKIs and the emergence of intrinsic tumor resistance mechanisms.[46] Moreover, mutations in the metastatic site may differ from those in the primary tumor in up to 33% of cases.[47] Furthermore, a multi-institutional retrospective study demonstrated that the use of upfront EGFR TKI therapy and deferral of radiation therapy (SRS or WBRT) was associated with inferior survival.[48] Likewise, a retrospective analysis from randomized trials in patients with BM and *ALK* rearrangement who were receiving crizotinib highlighted an increased median intracranial time to progression (TTP) for locally pretreated (with brain radiotherapy) patients (13.2 versus 7 months, respectively). Intracranial median TTP was 7 months and systemic TTP was 12.5 months in patients who did not receive brain-specific treatment. This underscores that brain is a main primary site of relapse in nonirradiated patients treated with a TKI with poor blood-brain barrier penetration.[49] However, an impressive median survival of 49.5 months was seen in 90 patients with NSCLC treated with both radiation (WBRT or SRS) and crizotinib.[50] It should be highlighted that 41 patients also received a second-generation ALK inhibitor and this may have accounted for the observed increased outcomes.

Second- and third-generation ALK inhibitors (ceritinib, alectinib, brigatinib, and lorlatinib) demonstrated a more favorable pharmacokinetic profile with greater CNS penetration.[46,51,52] Prospective research concerning the CNS activity of second- and newer-generation TKIs is ongoing. Possibly, these newer TKIs can change the need for local treatments. Striking results were reported with alectinib (a second-generation ALK inhibitor) at the 2017 American Society of Clinical Oncology meeting. In a phase III, open label, randomized trial comparing alectinib with crizotinib, the time to CNS progression was significantly longer with alectinib in the intention-to-treat population (cause-specific HR = 0.16, $p < 0.001$); 18 patients in the alectinib group (12%) had an event of CNS progression, as compared with 68 patients in the crizotinib group (45%). The cumulative incidence rate of CNS progression was consistently lower with alectinib than with crizotinib, and the 12-month cumulative incidence rate of CNS progression was 9.4% versus 41.4%. The median duration of intracranial response was 17.3 months (95% CI: 14.8–not estimable) and 5.5 months (95% CI: 2.1–17.3), respectively. Among patients with measurable or nonmeasurable CNS lesions at baseline, a CNS response occurred in 38 of 64 patients in the alectinib group (59%) and in 15 of 58 patients in the crizotinib group (26%); 29 patients in the alectinib group (45%) had a complete CNS response, as compared with five patients in the crizotinib group (9%). Therefore, it appears reasonable to delay the WBRT for brain metastatic *ALK*-translocated tumors in first-line treated with alectinib. It then seems reasonable to postpone WBRT in patients with NSCLC with targetable driver mutations. Whether the association of WBRT and specific TKIs (both in patients with *EGFR*-mutated NSCLC and in patients with *ALK*-rearranged NSCLC) could be synergistic is additionally evaluated in clinical trials (e.g., NCT01518621 or NCT02714010).

Patients without Targetable Driver Mutation

It is generally admitted that systemic treatments should be initiated in nonsymptomatic patients with multiple BMs; as with first-line chemotherapy, the

intracranial response rate is similar or only slightly lower than the extracranial response rate, resulting in deferral or omission of WBRT.[10] To improve outcomes, several chemotherapeutic regimens have been tested concurrently with WBRT in patients with NSCLC, but with disappointing results.[53–55] The role of temozolomide associated with WBRT in NSCLC is controversial. Although some studies have reported good response rates and limited toxicity,[56,57] others (including the prematurely stopped RTOG 0302 phase III trial) have demonstrated deleterious effects.[58,59]

In the context of the growing place of immune checkpoint blockers targeting the programmed cell death 1 axis in NSCLC,[60,61] preliminary data are becoming available for patients with BM. Pembrolizumab showed intracranial activity in six of 18 patients with NSCLC (33%) enrolled in a phase II trial.[62] Nivolumab, however, led to discontinuation of treatment on account of exacerbation of neurologic symptoms in seven of 12 patients with CNS metastasis who discontinued it [58%].[63] This could correspond to pseudoprogressive or hyperprogressive disease described in patients treated with anti–programmed cell death 1/programmed death ligand 1.[64,65] Whether WBRT may potentially limit this rare CNS effect or potentiate the efficacy of immunotherapy should be further evaluated in carefully selected patients.[66,67]

Prospects

Future Selection of Patients in Clinical Trials

All four randomized trials testing the role of adjuvant WBRT enrolled patients with several primary tumors. Although more and more studies for systemic therapies are based on specific biomarkers, most SRS and WBRT trials included a large variety of tumors that have nothing in common apart from the presence of BM. However, it should be emphasized that NSCLC represented most cases in almost all the trials of cranial irradiation. Even within the same histologic subtype, management is now driven by genetic profile. Selection of patients for adjuvant WBRT is a critical issue because the patients who would benefit are those with initially good neurocognitive function, young age, KPS of 70 or higher, low extracranial tumor burden, high DS-GPA or RPA score, or presence of *EGFR/ALK* alteration (Lung-molGPA).[35] The latter should also be discussed in light of newer-generation TKIs. Conversely, in patients with deteriorated baseline neurocognitive function, advanced age, poor KPS, high tumor

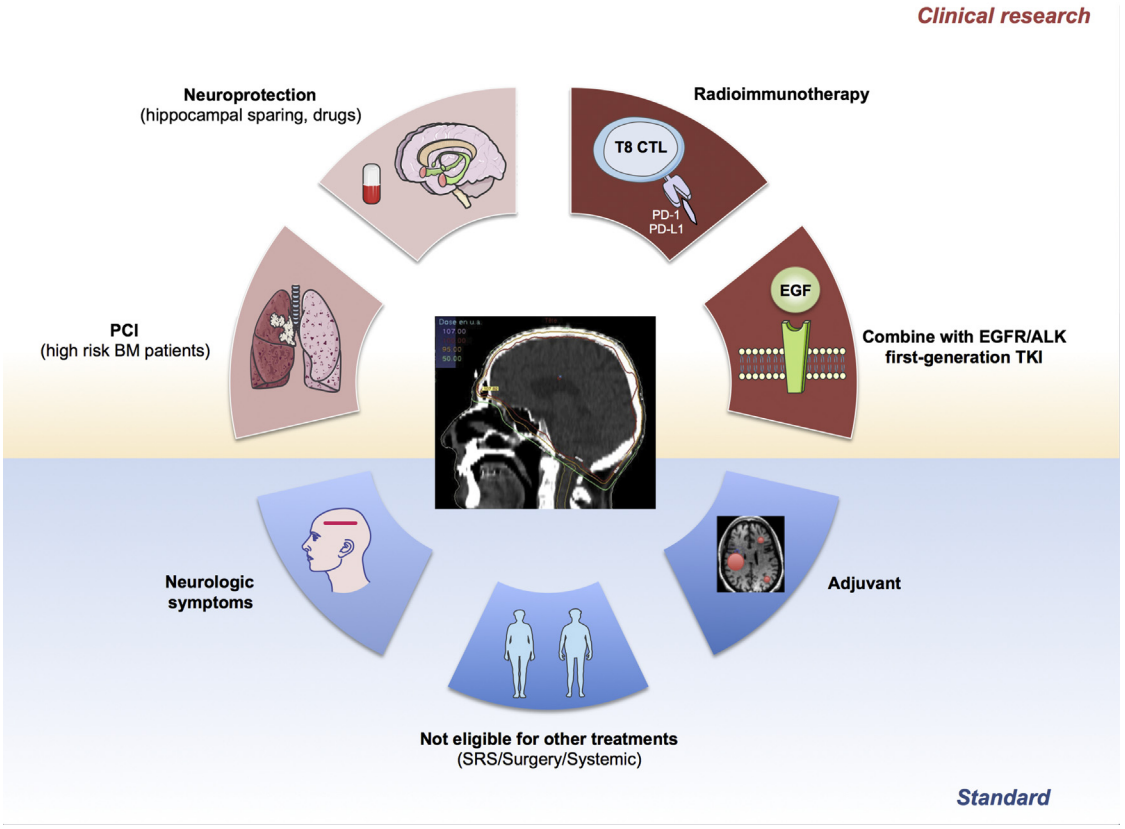

Figure 1. Possible spectrum of indications for whole brain radiotherapy in patients with NSCLC with multiple brain metastases (BMs). CTL, cytotoxic T lymphocyte; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; PCI, prophylactic cranial irradiation; EGF, epidermal growth factor; ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; SRS, stereotactic radiosurgery.

burden, and poor DS-GPA/RPA score, WBRT will not add any survival or QoL benefit and may even possibly hasten the death of frail individuals.

Expectations in Neuroprotective Strategies

The decreased neurocognitive function after brain irradiation may potentially link to damage of neural stems cells in the subventricular zone and hippocampus. Sparing hippocampi during WBRT by using intensity-modulated radiation therapy could theoretically reduce the neurocognitive impairment. This was first tested in the single-arm phase II trial RTOG 0933 (56 of 100 patients enrolled had lung cancer). This trial showed a mean relative decline of 7% in HVLT-revised delayed recall at 4 months, which represents a significant improvement as compared with the 30% decline of the historical control.[68] Two phase III trials (NCT02341170 and NCT02448992) are specifically assessing hippocampus-sparing PCI in locally advanced NSCLC.

Another strategy relies on the use of neuroprotective agents; it was tested in two randomized trials. The RTOG 0614 assessed memantine, an oral *N*-methyl-D-aspartate receptor antagonist, in patients with BM who were receiving WBRT. Patients were randomized to receive either placebo or memantine within 3 days of initiation of radiotherapy for 24 weeks. From 508 eligible patients (70% with lung cancer), only 149 were analyzable for the delayed recall at 24 weeks, which was the primary end point. There were fewer declines in delayed recall in the memantine arm at 24 weeks, but the difference was not statistically significant ($p = 0.06$). However, the memantine arm had a significantly longer time to cognitive decline and superior results regarding executive function at 8 and 16 weeks and processing speed.[69] The second trial enrolled a total of 198 adult patients with brain tumors who had survived for at least 6 months after partial or WBRT; they were randomly assigned to receive donepezil, a cholinesterase indicated in Alzheimer disease, or placebo. A cognitive composite score assessing memory, attention, language, visuomotor, verbal fluency, and executive functions was defined as the primary end point. After 24 weeks of treatment, the composite scores did not differ significantly between groups, but it resulted in modest improvements in several cognitive functions, especially among patients with greater pretreatment impairments.[70]

Conclusion

The indications for WBRT have decreased, whereas the indications for SRS have increased. WBRT still has a role to play in BM management of selected patients with multiple BMs (Fig. 1). To our viewpoint, and in accordance with European Society for Medical Oncology guidelines,[10] we discuss WBRT in symptomatic patients with NSCLC with multiple BMs (large BMs >3 cm and progressive small metastases with total BM volume >20 cm^3) and adequate DS-GPA (>1.5)/RPA (class I or II) scores. In patients without actionable oncogenic driver mutations, the main indications include neurologic symptoms and brain progression after/during front-line systemic chemotherapy. Adjuvant WBRT has become exceptional, as our preferred option is adjuvant SRS (residual tumor and larger size). CNS penetration of immune checkpoint blockers is currently a topic of intense search, and no firm suggestion can be made as yet. WBRT, as well as brain SRS, is postponed in patients with targetable driver mutation, but these patients should be closely monitored (brain magnetic resonance imaging every 2–3 months).[71] The role of WBRT will probably continue to evolve in the coming years. This will depend on the ability of newer systemic treatments to cross, alone or in combination, the blood-brain barrier. Optimization of WBRT with pharmacological and technical innovations to selectively spare organs involved in the memory process may also decrease the potential toxicity of WBRT.[72]

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